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Title

Dynamic Energy Budget Models in ecological risk assessment: From principles to applications

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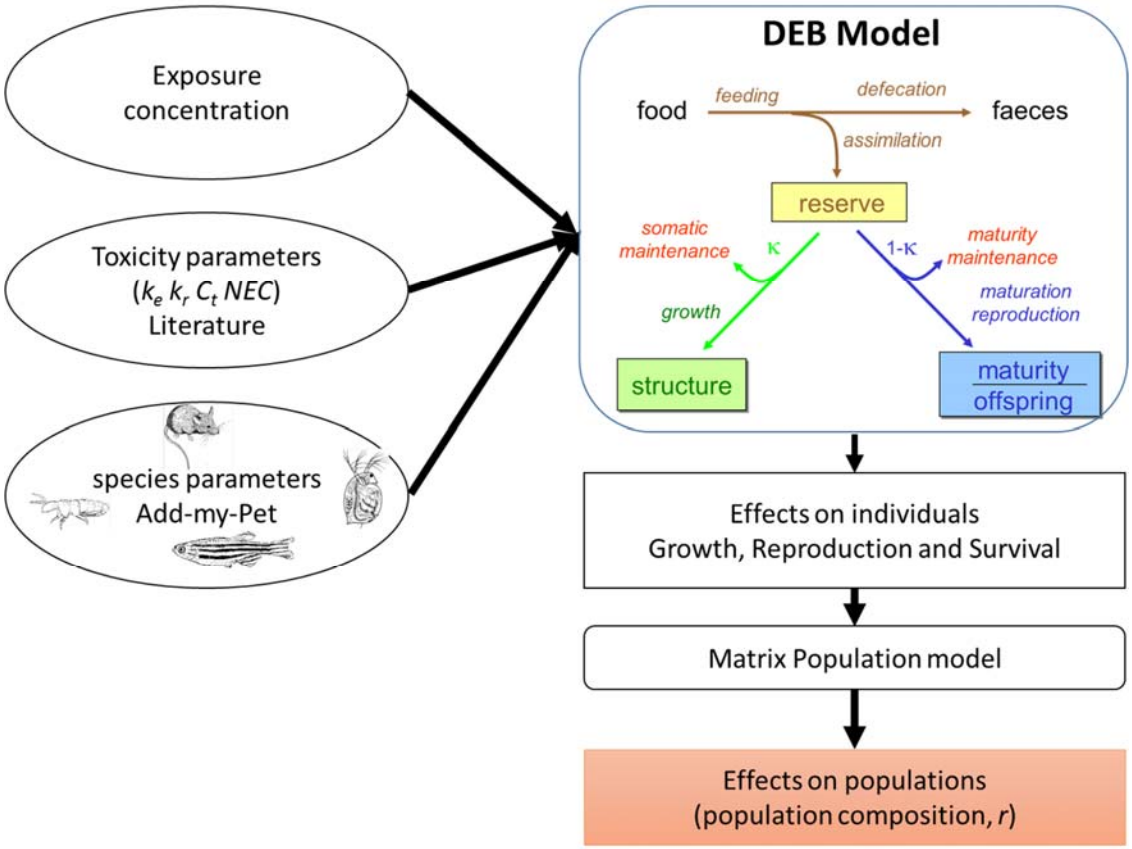
Abstract

In ecological risk assessment of chemicals, hazard identification and hazard characterisation are most often based on ecotoxicological tests and expressed as summary statistics such as No Observed Effect Concentrations or Lethal Concentration values and No Effect Concentrations. Considerable research is currently ongoing to further improve methodologies to take into account toxico kinetic aspects in toxicological assessments, extrapolations of toxic effects observed on individuals to population effects and combined effects of multiple chemicals effects. In this context, the principles of the Dynamic Energy Budget (DEB), namely the conserved allocation of energy to different life-supporting processes in a wide variety of different species, have been applied successfully to the development of a number of DEB models. DEB models allow the incorporation of effects on growth, reproduction and survival within one consistent framework. This review aims to discuss the principles of the DEB theory together with available DEB models, databases available and applications in ecological risk assessment of chemicals for a wide range of species and taxa.

Future perspectives are also discussed with particular emphasis on ongoing research efforts to develop DEB models as open source tools to further support the research and regulatory community to integrate quantitative biology in ecotoxicological risk assessment.

Graphical Abstract



Abbreviations

AmP: Add-my-Pet; DEB: Dynamic Energy Budgets; EFSA: European Food Safety Authority; LD_{50}: Lethal Dose for 50% of the individuals; LC_{50}: lethal concentration for 50% of the individuals; NOEC: No Observed Effect Concentration; NEC: No Effect Concentration; EC: Effect Concentration; EC_x: concentration with x% effect; ERA: Ecological Risk Assessment; TK: toxico-kinetic; TD: toxico-dynamic.

Highlights

- DEB theory is a framework for modelling time-specific lethal and sub-lethal effects.
- DEB models are promising tools for RA and have been applied to a variety of taxa.
- The Add-my-Pet database contains life cycle and DEB parameters for 857 species.
- Generic DEB models for RA are developed as open source tools as an EFSA project.

Keywords

Dynamic Energy Budget; ecological risk assessment; Add-my-pet; modelling; population dynamics

1 Introduction

Ecological risk assessment (ERA) of chemicals aims to characterise risks to the environment associated with chemical exposure combining an exposure and hazard dimension and to conclude on magnitude of effects that are deemed acceptable in relation to set protection goals (e.g. mortality). From a bird's eye view, frameworks for ERA often use tiered approaches which may depend on the aim of the assessment, the data available, and time-resources. For hazard identification and hazard characterisation, the first tier may use ecotoxicological endpoints from standardised laboratory experiments with aquatic and/or terrestrial species and at high tiers, results from semi-field to field trials. Using a first tier approach for hazard identification and hazard characterisation of regulated compounds (including pesticides and feed additives) assessments are often based on

summary statistics like the No-Observed-Effect-Concentration (NOEC), Lethal Dose (LD_{50}), Lethal Concentration for 50% of the exposed individuals (LC_{50}) or 50% Effect Concentrations on growth (or growth rate) and reproduction (or reproduction rate) (EC_{50}) for a specified exposure time. Environmental quality standards are then usually derived using the lowest available summary statistics for the NOEC LD_{50}, $EC_{50,}$ applying an uncertainty factor (UF) to derive a predicted no-effect concentration (PNEC). The UF that is applied depends on data availability but in most cases it is the standard default value of 100-fold UF. This default value may be replaced by data driven UFs depending of data availability on taxa specific toxicity such as chemical specific adjustment factors (CSAFs) applied in the human health area (WHO, 2005).

Over the last decade, considerable research efforts have been put together to further improve risk assessment methodologies particularly to take into account mechanistic understanding of toxicity. In the human risk assessment area, the **Mode of Action** (MoA) framework has been developed by the US-EPA and WHO as 'a biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data'. MoA describes in a logical framework key cytological and biochemical events that are both measurable and necessary to the observed effect. MoA does not imply full understanding of **Mechanism of Action** (MeA) which relates to a detailed molecular description of individual biochemical and physiological key events leading to a toxic effect (Boobis et al., 2006; Meek et al., 2014)). In toxicological terms, the MoA framework provides means to investigate toxico-kinetics (TK) and toxico-dynamic (TD) processes at different levels of biological organisation (organism, organ,

101 cellular and sub-cellular level). TK describes the processes leading to the internal
102 concentrations of a chemical or its metabolites(s) through knowledge of absorption (A),
103 distribution (D), metabolism (M) and excretion (E) (ADME). TD describes the processes
104 that lead to the toxic effects of a chemical or its metabolites(s) once it has reached the
105 organ(s) or tissue(s) (EFSA, 2014). In ERA, a number of MoA classifications have been
106 developed and include: 1. Verhaar classification using five broad categories based on
107 general toxicological responses: class 1. narcosis or baseline toxicity; class 2. less inert
108 compounds class 3 unspecific reactivity, class 4. compounds and groups of compounds
109 acting by specific mechanism, class 5.unknown mechanism, 2. the U.S. Environmental
110 Protection Agency (US-EPA) assessment Tool for Evaluating Risk (ASTER) MoA, 3. the
111 US-EPA Mode of Action and Toxicity (MOAtox) database providing a high degree of
112 specificity based on fish behavioural responses or weight of evidence classification
113 (Kienzler et al., 2017).
114 The related concept of **Adverse Outcome Pathway** (AOP) emerged from the field of
115 ecotoxicology and has been defined as 'a sequence of events from the exposure of an
116 individual or population to a chemical substance through a final adverse (toxic) effect at
117 the individual level (from a human health perspective) or population level (from an
118 environmental perspective)'(Ankley et al., 2010). AOPs that have been investigated and
119 depicted are available on the AOP Wiki tool (aopwiki.org). Recent reviews provide
120 strategies, principles and best practices (Villeneuve et al., 2014a; Villeneuve et al., 2014b).
121 The mapping of AOPs is a very active area of toxicological research and advances have
122 been made to bring AOP together into networks. A recent review provided a description of
123 an AOP network based on five reproductive and developmental toxicity-related AOPs for

124 fish and illustrations on how such AOP networks can inform the development and
125 refinement of laboratory assays (Knapen et al., 2015). Recently, (Teeguarden et al., 2016a)
126 have introduced the aggregate exposure pathway (AEP) as an intuitive framework to
127 organize exposure data including ADME/TK data. The AEP framework supports, while
128 making use of existing exposure models, the improvement of the generation, organization,
129 interpretation, modelling and prediction of data from exposure sciences including
130 ADME/TK information (Teeguarden et al., 2016b). In practice, the AEP also provides a
131 holistic exposure counterpart to the AOP framework and a flexible tool to integrate the
132 two frameworks together to apply risk-based, hazard-based, or exposure-based approaches
133 in chemical risk assessment (Teeguarden et al., 2016a).
134
135 In the food safety area, EFSA recently published a review on « Modern methods for human
136 hazard assessment of chemicals» which focused on mechanistic means to investigate TK
137 and TD processes for human risk assessment of chemicals. These included *in vitro* systems
138 to move towards the use of alternative approaches to animal testing, physiologically-based
139 (PB) models (such as PB-TK and PB-TK-TD models), and computer models including
140 (Quantitative) Structure Activity Relationship (Q)SAR) systems), read across methods as
141 well as OMICs technologies (transcriptomics, proteomics, and metabolomics) (EFSA,
142 2014). Consultation of EFSA experts and other international organisations identified
143 important needs to develop open source platforms for PB-based models to further explore
144 their applicability and integration in chemical risk assessment for single and multiple
145 chemicals (EFSA, 2013; EFSA, 2014). Specifically, the models should be calibrated using
146 specific case studies to illustrate the integration of exposure, TK information and toxicity

147 data, databases providing critical parameters to build these models (physico-chemical,
148 physiological, toxicological) and bioinformatic tools/algorithms to analyse and integrate
149 such data (EFSA, 2014).
150
151 In ERA, key empirical and mechanistic models have been developed over the last two
152 decades for terrestrial and aquatic species such as physiologically-based TK models (PB-
153 TK), physiologically-based TK-TD models (PB-TK-TD) (Grech et al.) and dynamic
154 energy budget (DEB) models which are the focus of this review. Here, the principles of the
155 DEB theory and standard DEB models are introduced together with the available databases
156 providing life cycle parameters to the standard DEB model. DEB models to assess impact
157 of chemicals and other stressors on organisms at the individual and population level are
158 then discussed with examples from the literature. Ongoing and Future work to develop
159 open source DEB models to support the ecotoxicological scientific community conclude.

160 ## 2. DEB theory and DEB models: Fuelling the life cycle with energy and mass from
161 ## individuals to populations

162 ### 2.1. DEB theory and the standard DEB model
163
164 Historically, the DEB theory finds its origin in 1979 in an ecotoxicology laboratory in the
165 Netherlands (Delft) investigating the toxicology of chemicals on daphnids and several
166 species of fish. The main question raised during these experiments was how to incorporate
167 growth and reproduction in a consistent quantitative framework that would apply to

different taxa? This was the starting point in the line of reasoning that kick started DEB theory.

The observation that growth curves of very different species like daphnia and fish are very similar in their appearance (typically characterised by Von Bertalanffy growth (Bertalanffy, 1938)), despite huge possible differences in the numbers along the axes, raises the question on the existence of underlying fundamental principles. The DEB theory deals with these underlying principles and describes how energy and mass from environmental resources are used over time to fuel the life cycle of an organism under physiological conditions (e.g. feeding, maintenance, growth, development and reproduction) into one consistent framework. Conservation of mass and energy as well as species specific stoichiometric constraints are also taken into account.

From the DEB theory, a number of families of related models have been derived with various levels of complexity. The complexity of the model (parameters and state variables) depends on the questions one is interested in and the availability and quality of data available. The simplest complete DEB model is the standard DEB model in which an organism consists of one structure and one reserve and feeds on one food source (see Figure 1) (Kooijman, 2010). The standard DEB model assumes that the shape of an organism from a particular species does not change during growth and that the life cycle is defined by three life stages: embryo, juvenile and adult.

figure 1 somewhere here

191 Figure 1 Schematic presentation of the standard DEB model

192 Boxes: state variables for the individual. Arrows: energy fluxes for the process specified

193 by the arrow

194

195 Figure 1 highlights that in the standard DEB model food is taken up by the organism and

196 is stored in reserves from which food is mobilized and used to grow, mature, reproduce

197 and maintain the integrity of the system. The use of the mobilized flux follows the so called

198 kappa-rule. The kappa-rule states that a fixed fraction of the available reserves is used for

199 growth and somatic maintenance and the remaining part is used for development, maturity

200 maintenance and reproduction. κ is assumed to be a constant over the lifetime of an

201 individual, this assumption implies that growth and reproduction do not compete directly

202 for resources. Embryos (which do not feed or reproduce) and juveniles (which feed but do

203 not reproduce) use the available energy from reserves for the development of physiological

204 systems and reproductive organs.

205 In each of these two branches priority is always given to maintenance: somatic maintenance

206 the κ branch and maturity maintenance in the $(1-\kappa)$ branch. If the rate of energy

207 utilisation from the reserves is no longer sufficient to sustain the maintenance costs, there

208 are several options depending on the species: the individual might die, it might

209 exceptionally use energy from the reproduction buffer or if possible it might shrink/lose

210 weight reducing the maintenance costs. As development stops at puberty, when a juvenile

211 organism becomes adult, the energy is then reassigned to fuel reproduction, typically in the

212 form of a reproduction buffer. When sufficient data are available and whenever needed,

213 the standard DEB model can be extended to incorporate biological traits for specific taxa

214 or default values under data poor conditions. For example, when developing DEB models
215 for plants, it is essential to introduce more than one structure or primary producers would
216 need more than one reserve (Kooijman, 2010). Different biological traits can be included
217 in the standard DEB model as extensions, with conservation of the interpretation of
218 parameters and parameter values.
219 Elaborate descriptions of the background of DEB theory and the fundamental mathematical
220 equations can be found in (Kooijman, 2010; Kooijman et al., 2008; Lika et al., 2011a; Lika
221 et al., 2011b; Meer, 2006; Sousa et al., 2010).

222 2.2 Linking the DEB parameters to standard life-cycle parameters

223 The eight parameters that describe the standard DEB model represent the energetics of an
224 organism and cannot be observed directly but can be derived from standard life-cycle data
225 (VU-Theoretical-Biology, 2017) such as:
226
227 -Time to hatching
228 -Body length at birth
229 -Weight at birth
230 -Growth rate
231 -Physical length at puberty
232 -Age at puberty
233 -Weight at puberty
234 -Time to first reproduction
235 -Final body length

-Final body weight

-Max reproduction rate

-Lifespan

Such life-cycle parameters then feed into the DEB model from which the underlying DEB parameters are derived (Lika et al., 2014; Lika et al., 2011a; Lika et al., 2011b). The overall quality of the data and the size of the database determine the extent to which the DEB parameters can be derived (Jager and Zimmer, 2012).

When the same group of organisms is followed over time in the laboratory, the resulting data are not independent. The model usually predicts reproduction as a continuous rate (e.g., number of eggs per day) for which a discrete number of offspring, produced by one or more females in a time interval, are observed. In addition, growth and reproduction are graded endpoints, whereas survival is a quantal endpoint. Although these endpoints are not directly comparable, they do share information about the same underlying parameters.

Any model is a simplification of reality and specifically biological data always show variation which creates scatter in the data. Therefore in any practical application much attention is given to the optimization procedure of estimating the parameters e.g. (Lika et al., 2011b).

2.3 DEB models coupling toxico-kinetics and energetics at the individual level: DEB-TOX and DEB-Kiss

2.3.1 The DEB tox model

The DEBtox model constitutes an application of the DEB theory to understand toxic effects and was first developed to address incorporation of different endpoints as the results of ecotoxicological testing. The link between TK/metabolism and toxic effects was first introduced in 1984 by Kooijman and Metz (Kooijman and Metz, 1984) who designed a model that already had most of the characteristics of the current DEB model except for the reserve dynamics. Later on the approach was further refined by Kooijman, Bedaux and Jager and co-workers (Jager et al., 2004; Kooijman and Bedaux, 1996). The general approach was adopted by the OECD in the guidance document dealing with "current approaches in the statistical analysis of ecotoxicity data: a guidance to application" (OECD, 2006). The main difference with classical ERA is that in classical ERA summary statistics from laboratory studies in standard test species are used. These include EC_{50} for growth (or growth rate), EC_{50} for reproduction (or reproduction rate), LC_{50} for survival and NOEC for growth and/or reproduction for a fixed exposure time depending on the species. By definition, single time-point summary statistics do not take into account TK and TD processes.

The DEBtox approach takes into account TK and TD processes. In the environment, organisms get exposed to chemicals and the first step leading to a pharmacological or toxicological effect is uptake from the environment (external dose) by the organism either through soil, air, water or food. Two critical processes are then involved namely "what the body does to the chemical": the TK, as the action of the body on the substance and "what the chemical does to the body": the TD, as the action of the substance on the body

(Benfenati et al., 2017; Spurgeon et al., 2010). Therefore a kinetic module should be the starting point for any further steps. In practice, an elimination rate (TK) is derived from the observed time course of toxicity (TD). In this context, the elimination rate does not necessarily reflect the whole body elimination but the rate determining step in linking internal concentrations to effects (TD) (Zitko, 1979).

The toxicant, once inside the organism and above some threshold level, may have an effect on growth, reproduction and or survival. This leads to the interpretation that toxicants result in physiological/toxicological modes of action, that affect life cycle traits by influencing (at least) one of the processes identified by DEB theory, see also figure 1 (Álvarez et al., 2006):

- increasing maintenance costs
- decreasing the assimilation of energy from food
- increasing the energetic costs for growing new body tissue
- increasing the energetic costs for producing offspring
- posing a direct hazard to the developing embryo

Recently, Ashauer and Jager (Ashauer and Jager, 2018) have defined these parameters as "*physiological MoA :a distinct way in which a chemical interferes with the energy fluxes in an organism, and thereby affects life-history traits*" including maintenance, assimilation, growth costs, reproduction costs and hazard to embryo. Here, the term DEB Mode of Action (DEBMoA) is applied since physiological mode of action may also be interpreted

302 in terms of physiology and not strictly speaking in toxicological terms as “adverse” with
303 regards to life cycle functions.
304
305 Three parameters are needed to describe the whole time-course of toxic effect (Kooijman
306 and Bedaux, 1996):
307
308 • A time-independent toxicological threshold below which no effects occurs
309 irrespective of exposure time the No Effect Concentration (NEC)), (as the incipient
310 LC_0). The NEC usually expressed as an environmental concentration).
311
312 • A TK parameter (k_e) which describes when the equilibrium between internal and
313 external concentration is set expressed in d^{-1}.
314
315 • A TD parameter that relates to the toxic potency of the compound; the killing rate
316 (k_r) expressed in $(mol/l)^{-1}day^{-1}$ for survival and the tolerance concentration (C_t) for
317 sub-lethal effects expressed in mol/l. The higher the killing rate and the lower the
318 tolerance concentration the more potent the toxicity of a compound.
319
320 From an ERA point of view, the threshold concentration is the most important parameter
321 (Baas et al., 2010a; Jager et al., 2006) and is also a more suitable metrics to compare species
322 sensitivity or the toxicity of different compounds compared with EC_x or LC_{50} values (Baas
323 and Kooijman, 2015; Jager et al., 2006). In fact EC_x or LC_x values can be calculated for
324 any value of x for any point in time using a DEB model coupled to a TK/TD module. By

325 making use of the DEB framework all parameters can be extrapolated from one species to
326 the next and ranges of biologically plausible values exist (Lika et al., 2014).
327
328 In all applications, integrated effects on growth and reproduction need to be translated to
329 the underlying DEB parameters and mechanism (Lika et al., 2011a; Lika et al., 2011b).
330 The overall quality of the data and the extensiveness of the dataset (body size over time,
331 timing of spawning events, number of offspring, survival over time) determines to what
332 extent this can be carried out. Still the mode of toxic action can be difficult to extract from
333 available data (Jager et al., 2014a; Muller et al., 2010a). Another practical consideration is
334 that the actual model parameters are calculated from their counterparts in the controls. So
335 having a reliable control is crucial to interpret which of the parameter values are affected
336 in order to derive the physiological mode of action.
337
338 With exposure above the threshold value toxic effects will develop over time, which is
339 mathematically interpreted as a change in parameter values in the affected process, defining
340 the DEBMoA. Each DEBMoA has specific consequences for the patterns of growth and
341 reproduction over the life cycle (Álvarez et al., 2006).
342 The survival module of the model can be used as a stand-alone part of the modelling
343 framework and consists of a scaled one-compartment model to describe uptake and
344 elimination and a hazard model to describe survival. This basically leaves out all the
345 energetics leading to a much simpler approach but it still gives a dynamic description of
346 the toxicity process, allowing to deal with e.g. time-dependent exposures and growth
347 dilution. In DEB theory the assumption is that death can be described by the hazard model,

348 contrary to the more frequently used LC_{50} where the underlying assumption is an Individual
349 Threshold (IT). When this threshold is reached the individual will die. In the hazard model
350 it is assumed that all species are equally sensitive and death is a chance process, whereas
351 in the IT approach it is assumed that the most sensitive ones die first. This has far reaching
352 consequences: if a cohort of individuals is exposed a second time to an LC_{50} concentration,
353 the IT model predicts no mortality in the second exposure and the hazard model predicts
354 again 50% mortality, like it was found in a dedicated experiment (Newman and
355 McCloskey, 2000). See also the description of the so called GUTS framework for survival
356 where an excellent description of the different approaches for survival is given and how
357 the different approaches relate to one another (Jager et al., 2011) and how the models can
358 be applied and extended (Ashauer et al., 2016; Ashauer et al., 2015).

359 ### 2.3.2 .The DEBkiss model

360 The DEBkiss model has been introduced recently in the literature for the interpretation of
361 ecotoxicological data. The DEBkiss model is similar to the historical Kooijman-Metz
362 model (Jager et al., 2013b; Kooijman and Metz, 1984) both exclude the reserve dynamics
363 so that metabolic memory is not included and predictions for species in conditions with
364 lack of food become troublesome (see figure 2). In general terms, the reserve dynamics
365 and the underlying mechanism is probably the most debated part of general DEB theory
366 (Meer, 2006). Advantages of the DEBkiss approach lie in the derivation of simpler models
367 in terms of number of state variables (Jager et al., 2013b). The loss of one or two state
368 variables comes at the cost of biological realism and extrapolation potential since the
369 DEBkiss model is more species and context specific compared with the standard DEB
370 model. Nonetheless, the DEBkiss approach has been very useful in helping understand

371 effects over time under complex exposure situations (like repeated pulsed or mixtures).
372 Moreover, if the kinetics of mobilising the reserves is fast and metabolic memory is not
373 needed (e.g. organisms are fed *ad libitum* for an ecotoxicological test), the DEBkiss model
374 can be applied as a simplified version of the standard DEB model, with a comparable
375 interpretation of ecotoxicological test results (Jager et al., 2013b). A direct comparison
376 between the two models showed similar predictions if toxic effects on individuals were
377 extrapolated to effects on the intrinsic population growth rate (Jager and Klok, 2010b) with
378 a slightly better extrapolation potential of the more elaborate model. Maturity of the
379 organism (i.e. the switch to start reproduction) is also generally excluded in DEBkiss
380 models however this can be included if needed.

381 Figure 2, somewhere here

382

383

384 Figure 2 Graphical representation of the DEBkiss model. Here all energetic costs for
385 growth, maintenance and reproduction are taken up from food uptake without first being
386 taken up as reserves.

387

388 Critically, as reserves are one of the cornerstones of standard DEB theory alongside
389 exploiting mass and energy conservation, care has to be taken in the interpretation and
390 comparison of different models derived by either DEBkiss or the standard DEB model.
391 Parameters have different interpretations (though the same parameter abbreviations are
392 used) depending on the framework and may impact on conclusions regarding hazard
393 characterisation of a chemical or stressor.

2.4 DEB population modelling

Effects on individuals can be substantially different from effects on populations. For instance, comparable reductions in reproduction due to toxic stress at an individual level were demonstrated to lead to very large differences in effects at the population level (Beaudouin et al., 2015; Martin et al., 2012). Population level effects are considered to be an important aspect of ERA but are not (yet) often taken into account routinely (Forbes and Calow, 1999; Forbes et al., 2010). There is a general consensus that DEB-based modelling offers a first step towards population modelling since key features of an individual organism's life-cycle impacting on the population (growth, reproduction and survival) are captured within a consistent and well tested theoretical framework (Ananthasubramaniam et al., 2015; Bacher and Gangnery, 2006; Jager et al., 2014a). Currently, DEB modelling, with a growing database, historical data and experience of use, can also be applied as a predictive *in silico* tool allowing to perform informed extrapolations of toxic effects for untested concentrations and other environmental conditions, such as food limitation.

Under constant environmental conditions (and excluding intra- and interspecific interactions and density effects), populations grow following an exponential model, with an asymptotic population growth rate (r) (Billoir et al., 2007; Forbes et al., 2010). The influence of toxicants on life-history traits (survival and reproduction) can directly be expressed as a decrease in r. Even though it is clearly unrealistic to expect prolonged exponential growth in real populations, r reflects the inherent capacity of a population to adapt to adverse effects or bounce back from a drastic decline in numbers. Therefore, r can be considered a general fitness measure for the population (Forbes et al., 2010). Note that

417 the underlying implicit assumption here is that each new generation will have identical
418 sensitivity. This is not necessarily the case, and sensitivity of later generations may be
419 substantially different as demonstrated recently in multi-generation studies and such
420 information may be accounted for in the population modelling, however, often not
421 available even though highly relevant to ERA (Biron et al., 2012; Schultz et al., 2016).
422
423 In general, steps for the modelling of individuals to the population level include rules for
424 interaction(s) between individuals and for the transport of resources in the environment.
425 The simplest interaction rule for the standard DEB model is that individuals only interact
426 via competition for resources. In the case of organisms that reproduce by division, the
427 transition from the individual to the population is much simpler and a population of a few
428 adult individuals may behave identically to that of many small ones if the sum of their
429 masses matches. Here, the individual level is not critical but the population itself
430 (Kooijman, 2010). This was used in Poggiale et al. (Poggiale et al., 2010), where
431 population performance was directly linked to sub-individual physiology. There are
432 various DEB based applications to extrapolate toxic effects on individuals to populations
433 using different types of population models and these are either based on complete DEB
434 models or simplified approaches (Alver et al., 2006; Ananthasubramaniam et al., 2015;
435 Bacher and Gangnery, 2006; Beaudouin et al., 2015; Billoir et al., 2007; Biron et al., 2012;
436 Jager and Klok, 2010a; Klanjscek et al., 2006; Kooijman et al., 1989; Martin et al., 2014;
437 Martin et al., 2013; Martin et al., 2012; Nisbet et al., 2010).

3. Databases and Tools for DEB modelling

DEB modelling is applicable when the relevant variables can be generated such as the No Effect Concentration (NEC) which constitutes a model parameter that can be interpreted and applied in ERA. In other cases, dynamic simulation studies might be required and the DEB model might have to be coupled to fate and transport models or parameters controlling offspring production integrated into population level models (see above population models) (Kooijman, 2012). Figure 3 illustrates a generic DEB population modelling approach under which species and compound properties as well as toxic effects feed into the standard DEB model for individuals as DEB-modes of action (such as an effect on assimilation) and output parameters modulated by the toxicant. The general output of the population DEB model is given as the survival probability of the individuals and the impact on reproduction.

Figure 3 somewhere here

Figure 3 Schematic representation of DEB population modelling. The ellipses are input data, the boxes the different models and the rounded boxes model output.

3.1 Add My Pet: A Database for DEB modelling

DEB parameters describing the energetics of species cannot be derived directly from observations on species but are estimated using the underlying life history parameters (as was described in section 2) and these together define the underlying DEB parameters.

460 Information and quantitative data on the eco-physiology and life-history traits of different
461 species can be collected from several major databases: Add-my-Pet, Animal Diversity
462 Web, Encyclopedia of Earth and Fish Base (Kooijman et al., 2017).
463
464 The Add-my-Pet (AmP) database summarises the underlying energetics that together
465 capture life history data, to derive DEB parameters. AmP is a pan European initiative and
466 is extensively documented using collaborative online media wiki powered software. For
467 this reason, AmP is the natural information base for supporting ERA of single and multiple
468 chemicals. Other databases (Animal Diversity Web, Encyclopedia of Earth and Fish Base)
469 are typically used for life cycle data, which are then used to generate DEB parameters for
470 more species to populate the AmP database.
471 AmP is an initiative, which started in 2009, in the context of much wider aims than ERA:
472 find the simplest organisation principles for metabolism upon which all life is based and
473 understand taxon-specific patterns as variations on this common theme. It turned out that
474 a number of extensions on the standard DEB model were needed to capture specific life-
475 history of various groups of species. The overall model can therefore vary from taxa to taxa
476 but it is also possible to use different extensions of the standard model for a single species
477 depending on the level of refinements one wants the model to achieve. This approach can
478 be followed without any loss of consistency and parameter values can be compared for
479 different species. Some examples of model extensions are relaxing the assumption of
480 constant shape whereby changes in shape allow metabolism to accelerate for part of the
481 life-cycle. Or including extra-life stages (for instance weaning for mammals), reversing the
482 order of life-stages (adults come before embryos for insects), and choosing different modes

483 of reproduction (foetal or egg development). Parameters values for the different species
484 remain comparable for the different variations.

485 The AmP collection contains data for 871 species (AmP, 2017/06/12) from all of the large
486 phyla excluding sponges (cnidaria) (see figure 4). Furthermore, there are species belonging
487 to each chordate order, with the exception of some deep water ray finned fish and marsupial
488 moles. Finally, there are species from all of the primate families. The standard DEB model
489 assuming either egg or foetal development captures the life-history of about two thirds of
490 the taxa present in the collection quite well.

491 Figure 4, somewhere here

492

493 Figure 4 Overview of species in Add-my-Pet and the number of species included in Add
494 my-pet over time (06/12/2017)

495 ### 3.2 Ecotoxicological Databases and QSAR models

496 For effects on survival, DEB toxicity parameters can be derived if LC_{50} values are
497 available at different points in time or by making use of QSARs (Baas et al., 2015; Jager
498 and Kooijman, 2009).

499

500 Most available databases report single time point toxicity data, which have yet limited
501 applications in process-based approaches or TK-TD modelling. The ECOTOX database,
502 hosted by the United States Environmental Protection Agency (US-EPA, 2013) is currently
503 the most complete database existing for which a plethora of toxicity data published in the

scientific literature have been gathered and summarised, including some LC_{50} data for multiple points in time. The US-EPA ECOTOX database has been extensively used for the determination of DEB parameters for survival for pesticides using multiple points in time which are present for a limited number of substances (Baas et al., 2009a; Baas et al., 2016a). For sub-lethal toxicity, the time course of toxic effects is not straightforward and parameters have not been derived from EC_{50} data over time (Baas et al., 2010a; Jager et al., 2006).

The Pesticide Property Database (PPDB) is a comprehensive relational database of pesticide chemical identity, physicochemical, human health and ecotoxicological data. It contains data on all pesticides that are allowed in the EU and contains data on 1150 pesticides, 700 metabolites and some 100 related compounds. It has been developed by the Agriculture & Environment Research Unit (AERU) at the University of Hertfordshire for a variety of end users to support risk assessments and risk management (Lewis et al., 2016). The database is fed with pesticide properties based on the monographs produced as part of the EU review process published by EFSA. Where EFSA documents are not available, alternative sources are used. This implies that the vast majoriy of the data is well documented and measured according to the latest ISO regulations.

4. Applications of DEB models in ERA

The potential combinations of species and chemicals that may be present in a particular ecosystem is vast and performing ERA represents a challenge because of such complexity and the limited quantitative knowledge on a wide range of taxa specific traits. Most often, ERA is based on inter-species extrapolations where default uncertainty factors are applied

527 to account for lack of knowledge on inter-species TK and TD and allow site specific ERA.
528 In general terms, extrapolation operates (i) from individual to population (section 4.1), (ii)
529 from species to species (section 4.4), (iii) from chemical to chemical (particularly for
530 compounds that are structurally related) (section 4.3), (iv) from a single chemical to
531 mixtures of chemicals (section 4.2). Since data for sub-lethal effects are often scarce (see
532 section 3), (v) extrapolation are from lethal effects sub-lethal effects are most common.
533 The DEB theory allows to perform extrapolations (i) to (iv) but to our knowledge, the
534 derivation of sub-lethal effects from lethal effects has not been explored yet. However,
535 options are available for such extrapolations to be performed using TK parameters that are
536 derived from time course toxicity studies for lethal and sub-lethal effects using DEB theory
537 and other frameworks for extrapolations (Hendriks and Heikens, 2001; Hendriks et al.,
538 2001). Specifically, the DEB theory provides a means to quantify parameters related to
539 how individuals progress their way through life and how stressors affect specific parameter
540 values. Species properties (taxa-specific traits) are combined with physical (conservation)
541 and chemical (stoichiometry) constraints so that all measurable endpoints such as growth
542 and feeding are interlinked “there is 'no free lunch” (Jager et al., 2013a) and the
543 response/sensitivity of an organism is deeply linked to the metabolic evolution of the
544 organism survival in its specific environment. Finally, DEB models also allow the
545 incorporation of effects resulting from exposure to non-chemical stressors such as food
546 availability, temperature, salinity, parasites, etc.
547
548 In this context, a concise overview of taxa-specific and chemical specific DEB models is
549 provided below. For this purpose, an extensive literature search was performed in a number

550 of databases (SCOPUS, Faculty of 1000, ZETOC, Elsevier, Medline/PubMed, Springer
551 link, Taylor and Francis Crossref, GALE, AGRIS, Wiley, AIP, JSTOR, Picarta, Web of
552 Knowledge and Web of science) to report two board categories of case studies:
553
554 • Research investigating effects of chemicals on taxa-specific lethal and sub-lethal
555 endpoints for single and multiple chemicals, with a focus on the availability of TK
556 and TD parameters that could serve as input for population dynamics modelling
557 based on DEB theory. The separation of TK and TD provides a quantitative
558 understanding of TK parameters over time linked to TD and compared with
559 controls);
560 • Case studies providing means to extrapolate individual effects on single species to
561 a population.
562
563 Key words included in the extensive literature search included:
564
565 • DEB
566 • Dynamic Energy Budget
567 • Mixtures
568 • Ecotoxicology
569 • Modelling
570 • Mortality
571 • Growth
572 • Reproduction

- Population Dynamics
- Individual based modelling

Assessment criteria

- Consistency
- Method, full description, source code available?
- Biological relevance
- Study design, was the model applied to measured data and how
- Parameterization of the model, do the parameters relate to biological traits?
- Biological relevance, do the parameters relate to biological traits
- Application to bio-assays

The number of papers extracted from the extensive are summarised in table 1.

Application	**Nr of papers (after first selection)**	**Nr of relevant papers (after final selection)**
DEB in ecotoxicology	27	18
DEB in mixtures	13	7
DEB in population dynamics	36	15

Table 1 Summary of results of the literature survey

The sections below provide summary tables for taxa specific DEB models and applications.

4.1 Taxa-specific DEB–based approaches to model toxico-kinetics and toxico-dynamics of chemicals

Taxa-specific DEB based approaches to model TK ad TD impact of chemicals are given in table 2 and illustrates applications to a wide variety of aquatic taxa/species and shows limited data for terrestrial organisms. The diversity of taxa that have been modelled using these DEB approaches ranges from annelid and nematode worms, arthropods, mussels, daphnia and fish, however, the chemical space covered is still rather specific with most of the models developed on metals, pesticides and a few contaminants.

Phylum	**Species**	**Stressor (s)**	**DEB Model**	**Reference**
Annelida	*Dendrobaena octaedra*	Copper	DEBkiss	(Jager and Klok, 2010b)
Annelida	*Dendrobaena octaedra*	Copper	DEBtox	(Jager and Klok, 2010b)
Annelida	*Dendrobaena octaedra*	Copper	DEB	(Jager and Klok, 2010b)
Arthropoda	*Chironomus riparius*	Methiocarb	DEBMatrix population	(Lopes et al., 2005)
Bacteria	*Pseudomonas aeruginosa*	Cadmium	DEB hazard	(Klanjscek et al., 2012)

Chordata	*Danio rerio*	Uranium	DEB	(Augustine et al., 2012)
Copepoda (arctic)	*Calanus glacialis and Calanus finmarchicu*	PAHs	DEB	(Klok et al., 2012)
Crustacea	*Daphnia magna*	Cadmium	DEB Matrix population	(Billoir et al., 2007)
Crustacea	*Daphnia magna*	Uranium	DEBMatrix population	(Biron et al., 2012)
Crustacea	*Daphnia magna*	Fluoranthene	DEBkiss	(Jager and Zimmer, 2012)
Crustacea	*Daphnia magna*	3,4-dichloroanniline	DEB IBM	(Martin et al., 2012)
Mollusca	*Mytilus gallopro-Vincialis*	ZnO nanoparticles	DEB	(Muller et al., 2014)
Nematoda	*Acrobeloides nanus*	Pentachlorobenzene	DEB	(Álvarez et al., 2006)
Nematoda	*Acrobeloides nanus*	Carbendazim	DEB	(Álvarez et al., 2006)

Nematoda	*Acrobeloides nanus*	Cadmium	DEB	(Álvarez et al., 2006)
Nematoda	*Caenorhabditis elegans*	Uranium	DEB	(Goussen et al., 2015)
Nematoda	*Caenorhabditis elegans*	Aldicarb	DEB	(Wren et al., 2011)
Various	*Various (mussels, oysters, earthworms, water fleas and zebrafish)*	Various (mercury, copper, chlorophenols, toluene, PAHs, tetradifon, pyridine)	DEB	(Muller et al., 2010a)
Various	*Various (mussels, oysters, fish, water fleas)*	Pesticides (carbofuran, carbaryl, Chlorpyrifos, Malathion)	DEB	(Baas and Kooijman, 2015)

601 Table 2 Overview of Taxa-specific DEB models available in the literature including model
602 type (matrix population models, Individual based population models, hazard indicates
603 only survival).
604

4.2 Modelling toxico-kinetics and toxico-dynamics of multiple chemicals using DEB modelling

DEB models provide useful tools to model the combined toxicity of multiple chemicals. This specific application of DEB models was recently discussed as part of EFSA 's colloquium on "Harmonisation of human and ecological risk assessment of combined exposure to multiple chemicals" (EFSA, 2015). DEB based models have been developed for the interpretation and prediction of combined toxicity of chemical mixtures providing means to improve extrapolation potential. As with single toxicants, the temporal dynamics of combined effects induced by a chemical mixture on endpoints like survival or growth are not quantifiable using data from single time-point dose-response experiments. DEB models are intrinsically "biology based" and are essential for developing explicit hypothesis on mixture effects using dose addition as the default assumption or analysing evidence for interaction that may increase (synergy) or decrease toxicity (antagonism) (Baas et al., 2010).

In practice, a distinction can be made between DEB models for survival and DEB models for sub-lethal effects that usually also include effects on survival. Models investigating mixture effects on survival have been first developed for binary mixtures as component-based approaches (Baas et al., 2007) and were subsequently further developed to model effects of more complex mixtures with comparable constituents (Baas et al., 2009a; Baas et al., 2010b). Further development of DEB models then focused on actual complex environmental mixtures with up to 100 different constituents (including metals, pesticides, salts, nutrients, PAHs) (Baas et al., 2009b). For each model, predictions were compared

628 with available data. Models investigating sub-lethal mixture effects were first developed
629 from binary mixtures with similar mode of action (2 PAHs) (Jager et al., 2010). These have
630 been now generalised to binary mixtures for mixtures with a different modes of action
631 (Jager et al., 2014b; Margerit et al., 2016) and such a generic approach is illustrated in in
632 Figure 5.

633 Figure 5, somewhere here

634

635 Figure 5. Generic approach for modelling combined effects of chemical mixtures within
636 the framework of DEB theory.

637

638 In principle, every chemical entity is characterised with its own TK and toxicity (TD)
639 which may affect one or more DEB parameters. This is translated in the general DEB model
640 to an effect on life-cycle traits such as body size (growth), reproduction and survival. Note
641 that some interactions may take place physiologically as metabolic processes are often
642 ruled by feedback loops affecting on growth and reproduction. Synergistic effects may
643 occur under food limitation and exposure to toxicants thereby affecting maintenance and
644 somatic growth, as they compete for the same allocated reserves (Jager et al., 2014b). In
645 addition, body size determines feeding rate which feeds back to body size and body size in
646 itself affects TK and the initiation and rate of reproduction. A chemical in a mixture
647 producing adverse effects on growth of the exposed organisms may affect the TK of its
648 neighbour mixture components and their effects on reproduction. A list of DEB based
649 applications investigating combined toxicity of mixtures is given in Table 3.

650

651

Phylum	**Species**	**Stressor (s)**	**DEB Model**	**Reference**
Arthropoda	*Tribolium castaneum*	PAH	DEB mixture survival	(Baas et al., 2010b)
Arthropoda	*Folsomia candida*	Copper, Cadmium, Lead, Zinc	DEB mixture survival	(Baas et al., 2007)
Chordata	*Pimephalus promelas*	Narcotics	DEB mixtures survival	(Baas et al., 2009a)
Crustacea	*Daphnia magna*	Mixture of toxicants	DEB mixtures survival	(Baas et al., 2009b)
Crustacea	*Daphnia magna*	Mixture of toxicants	DEB mixtures survival	(Baas et al., 2016b)
Crustacea	*Daphnia magna*	Binary mixture PAHs	DEB (mixture)	(Jager et al., 2010)
Mollusca	*Mytilus gallopro-*	Produced water	DEB	(Muller et al., 2010b)

	vincialis and M. californianus			
Nematoda	*Caenorhabditis elegans*	Cadmium Fluoranthene	DEBkiss mixture	(Jager et al., 2014b)
Nematoda	*Caenorhabditis elegans*	Uranium Cadmium	DEB mixture	(Margerit et al., 2015)

652 Table 3 Applications of DEB theory for modelling combined toxicity of chemical mixtures

653 ### 4.3. Using DEB models for read across between species and chemical and natural stressors

654 Several DEB based publications demonstrated that good results in toxicity predictions for
655 compounds with no experimental data available or for inter-species extrapolation in data-
656 sparse conditions. This has been illustrated for a wide range of chemicals including metals,
657 narcotics and various kinds of pesticides as well as impact of food limitation or temperature
658 stress both on an individual and on a population level.

659

660 The DEBtox approach, particularly in the context of exposure chemical mixtures, is often
661 challenged for requiring a 'substantially higher data demand' compared with standard
662 approaches e.g. (Backhaus et al., 2013). This holds true for the characterisation of LC_x or
663 EC_x values for mixtures based on fixed time-points as well for more elaborate experimental
664 designs often lacking experimental data and requiring simplification of models (Jager et
665 al., 2014a). However, the DEB modelling approach has an important asset providing a
666 quantitative tool to test mixture toxicity for any x value in LC_x or EC_x (including zero)
667 without the need to assess 50% effect level for random time point which may vary widely

668 across species. Most often, environmental risk assessors would then need to apply a safety
669 factor as 50% of effect may be considered too high and not protective enough for the taxa.
670 If the standard mixture models are applied to assessments other than the fixed time 50%
671 effect level, they then become substantially more data intensive compared with the DEB-
672 based approach. In addition, a successful approach has been developed to predict combined
673 toxicity of a real life complex environmental mixture based on the TK-TD based DEB
674 approach, readily available data combined with read across and QSAR applications (Baas
675 et al., 2009b). In this case, standard methods to model mixture toxicity namely
676 Concentration addition (CA) (Hewlett and Plackett, 1959) and Independent action (IA)
677 (Bliss, 1939) both failed to make reliable predictions for the complex environmental
678 mixture.
679
680 Finally, DEB models do not have the flaw of a single time point LC_{50} 48 hr which may
681 need to be extrapolated to different exposure time. This also holds true for the extrapolation
682 between mixture exposure expressed as toxic units to the effect size (i.e. here percentage
683 of effect) (Baas et al., 2016b). Table 4 gives an overview of this application of DEB theory,
684 including effects of temperature and food limitation.
685
686

Phylum	**Species**	**Stressor (s)**	**DEB Model**	**Reference**
Chordata	*Merluccius merluccius*	PCB accumulation	DEB	(Bodiguel et al., 2009)
Chordata	*Danio rerio*	Population growth	DEB IBM	(Beaudouin et al., 2015)

Copepoda	*Calanus sinicus*	Temperature	DEBkiss	(Jager et al., 2015)
Crustacea	*Daphnia magna*	Food limitation	Matrix Simplified DEB	(Nisbet et al., 2010)
Crustacea	*Daphnia magna*	Pesticide mixtures	DEB mixture survival	(Baas et al., 2016b)
Crustacea	*Daphnia magna*	Pesticide mixtures	DEB mixture survival	(Baas et al., 2009b)
Mollusca	*Crassostrea gigas*	Harvesting oysters	DEB IBM	(Bacher and Gangnery, 2006)
Mollusca	*Lymnea stagnalis*	Food limitation	DEB	(Zimmer et al., 2012)
Mollusca	*Lymnea stagnalis*	Food limitation	DEBkiss	(Jager et al., 2013b)
Mollusca	*Macoma Balthica*	population dynamics	Lotka DEB	(Kooi and van der Meer, 2010)

Table 4 The use of DEB theory in data sparse conditions and for non-standard stressors like temperature or food limitation

4.4 Using DEB models to quantify interspecies differences in toxico-kinetics and toxico-dynamics of chemicals

Recently, DEB-based models have been developed to quantify interspecies differences in TK and TD and are summarised in table 5. For example, chronic time–course toxicity bioassays (10-day) have been performed in three bee species (honey bee, solitary bee and

695 bumble bee) for six chemicals and six mixtures and survival DEB-models were fitted to
696 the experimental data to determine the elimination and killing rate of the individual
697 compounds and mixtures. To date, these results provided the first time-course chronic
698 datasets and inter species comparison for three bee species (Heard et al., 2017; Hesketh et
699 al., 2016; Robinson et al., 2017).
700
701

Phylum	**Species**	**Stressor (s)**	**DEB Model**	**Reference**
Arthropoda	*Apidea*	Pesticides/metals	DEB survival	(Hesketh et al., 2016)
Arthropoda	*Apis mellifera, Bombus terrestris, Osmia bicornis*	Pesticides/metals	DEB survival	(Heard et al., 2017)
various	*Various*	narcotics	DEB survival	(Baas et al., 2015)
various	*Various*	pesticides	DEB survival	(Baas and Kooijman, 2015)

702 Table 5. DEB-based models investigating interspecies differences in toxico-kinetics and
703 toxico-dynamics

5. Future directions and conclusions

This review provides an account of the DEB theory and applicability of DEB models to assess chemical toxicity on individuals and population dynamics of aquatic and terrestrial organisms. A key component of the approach is the separation of TK and TD processes, which provides (1) elimination rate as a key TK parameter, (2) time-independent toxicity parameters describing toxic effects for different endpoints and integrating them within one consistent framework using databases such add my pet providing parameters for the standard DEB model. As a consequence, DEB models also provide a tool to quantify interspecies differences in TK and TD processes thus providing a basis for predictive modelling across taxa and chemical space.

In order to further enhance the applicability of generic DEB models for the modelling of population dynamics in terrestrial and aquatic organisms, a collaborative project between EFSA (Italy), the Centre for Ecology and Hydrology (UK), the High North Research Centre for Climate and the Environment (Norway) and Terraprima (Portugal) is exploring the development of open source DEB tools in R and their Applications in ERA for modelling toxicity of single and multiple chemicals at the individual and population level. This project further support the application of biologically-based models in ERA including PB-TK models as review elsewhere (Gresh et al., 2016).

Further work is recommended in this area to further support the application of biologically-based models in ERA including: 1. Development of open source databases providing *taxa specific parameters* (physiological parameters, molecular information on taxa specific

traits (e.g. receptor sequences, adverse outcome pathways etc..) and *chemical specific parameters* (physico-chemical properties, toxicity and TK parameters etc..). 2. Design of toxicity studies should be designed to provide and understanding of both TK and TD dimension to provide time-independent toxicological threshold, elimination rate of the compound and potency information on the compound. Examples of such study designs include the recent interspecies comparison studies in honey bees, solitary bees and bumble bees to investigate chronic toxicity (10 day) of pesticides and contaminants (single and mixtures).

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Disclaimer

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References

Álvarez OA, Jager T, Redondo EM, Kammenga JE. Physiological modes of action of toxic chemicals in the nematode Acrobeloides nanus. Environmental Toxicology and Chemistry 2006; 25: 3230-3237.

Alver MO, Alfredsen JA, Olsen Y. An Individual-based Population Model for Rotifer (Brachionus plicatilis) Cultures. Hydrobiologia 2006; 560: 93-108.

Ananthasubramaniam B, McCauley E, Gust KA, Kennedy AJ, Muller EB, Perkins EJ, et al. Relating suborganismal processes to ecotoxicological and population level

752 endpoints using a bioenergetic model. Ecological Applications 2015; 25: 1691-
753 1710.
754 Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, et al. Adverse
755 outcome pathways: A conceptual framework to support ecotoxicology research
756 and risk assessment. Environmental Toxicology and Chemistry 2010; 29: 730-741.
757 Ashauer R, Albert C, Augustine S, Cedergreen N, Charles S, Ducrot V, et al. Modelling
758 survival: exposure pattern, species sensitivity and uncertainty. Scientific Reports
759 2016; 6: 29178.
760 Ashauer R, Jager T. Physiological modes of action across species and toxicants: the key to
761 predictive ecotoxicology. Environmental Science: Processes & Impacts 2018.
762 Ashauer R, O'Connor I, Hintermeister A, Escher BI. Death Dilemma and Organism
763 Recovery in Ecotoxicology. Environmental Science & Technology 2015; 49: 10136-
764 10146.
765 Augustine S, Gagnaire B, Adam-Guillermin C, Kooijman SALM. Effects of uranium on the
766 metabolism of zebrafish, Danio rerio. Aquatic Toxicology 2012; 118–119: 9-26.
767 Baas J, Jager T, Kooijman B. Understanding toxicity as processes in time. Science of The
768 Total Environment 2010a; 408: 3735-3739.
769 Baas J, Jager T, Kooijman SALM. A model to analyze effects of complex mixtures on
770 survival. Ecotoxicology and Environmental Safety 2009a; 72: 669-676.
771 Baas J, Kooijman SALM. Sensitivity of animals to chemical compounds links to metabolic
772 rate. Ecotoxicology 2015; 24: 657-663.
773 Baas J, Spurgeon D, Broerse M. A simple mechanistic model to interpret the effects of
774 narcotics. SAR and QSAR in Environmental Research 2015; 26: 165-180.
775 Baas J, Stefanowicz AM, Klimek B, Laskowski R, Kooijman SALM. Model-based
776 experimental design for assessing effects of mixtures of chemicals. Environmental
777 Pollution 2010b; 158: 115-120.
778 Baas J, Van Houte BPP, Van Gestel CAM, Kooijman SALM. Modeling the effects of binary
779 mixtures on survival in time. Environmental Toxicology and Chemistry 2007; 26:
780 1320-1327.
781 Baas J, Vijver M, Rambohul J, Dunbar M, van't Zelfde M, Svendsen C, et al. Comparison
782 and evaluation of pesticides monitoring programmes using a process based
783 mixture model. Environmental Toxicology and Chemistry 2016a: n/a-n/a.
784 Baas J, Vijver M, Rambohul J, Dunbar M, van 't Zelfde M, Svendsen C, et al. Comparison
785 and evaluation of pesticide monitoring programs using a process-based mixture
786 model. Environmental Toxicology and Chemistry 2016b: n/a-n/a.
787 Baas J, Willems J, Jager T, Kraak MHS, Vandenbrouck T, Kooijman SALM. Prediction of
788 daphnid survival after in situ exposure to complex mixtures. Environmental
789 Science and Technology 2009b; 43: 6064-6069.
790 Bacher C, Gangnery A. Use of dynamic energy budget and individual based models to
791 simulate the dynamics of cultivated oyster populations. Journal of Sea Research
792 2006; 56: 140-155.
793 Backhaus T, Altenburger R, Faust M, Frein D, Frische T, Johansson P, et al. Proposal for
794 environmental mixture risk assessment in the context of the biocidal product
795 authorization in the EU. Environmental Sciences Europe 2013; 25: 4.

796 Beaudouin R, Goussen B, Piccini B, Augustine S, Devillers J, Brion F, et al. An Individual-
797 Based Model of Zebrafish Population Dynamics Accounting for Energy Dynamics.
798 PLoS ONE 2015; 10: e0125841.
799 Benfenati E, Como F, Manzo M, Gadaleta D, Toropov A, Toropova A. Developing
800 innovative in silico models with EFSA's OpenFoodTox database. EFSA Supporting
801 Publications 2017; 14: 1206E-n/a.
802 Bertalanffy Lv. A qantitaive theory of organic growth (Inquiries on growth laws. II). Human
803 Biology 1938; 10: 181-213.
804 Billoir E, Péry ARR, Charles S. Integrating the lethal and sublethal effects of toxic
805 compounds into the population dynamics of Daphnia magna: A combination of
806 the DEBtox and matrix population models. Ecological Modelling 2007; 203: 204-
807 214.
808 Biron P-A, Massarin S, Alonzo F, Garcia-Sanchez L, Charles S, Billoir E. Population-Level
809 Modeling to Account for Multigenerational Effects of Uranium in Daphnia magna.
810 Environmental Science & Technology 2012; 46: 1136-1143.
811 Bliss CI. The toxicity of poisons applied jointly. Annals of Applied Biology 1939; 26: 585-
812 615.
813 Bodiguel X, Maury O, Mellon-Duval C, Roupsard F, Le Guellec A-M, Loizeau V. A dynamic
814 and mechanistic model of PCB bioaccumulation in the European hake (Merluccius
815 merluccius). Journal of Sea Research 2009; 62: 124-134.
816 Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, et al. IPCS framework
817 for analyzing the relevance of a cancer mode of action for humans. Crit Rev Toxicol
818 2006; 36: 781-92.
819 EFSA. Guidance on tiered risk assessment for plant protection products for aquatic
820 organisms in edge-of-field surface waters. EFSA Journal 2013. European Food
821 Safety Authority, Parma, Italy, 2013.
822 EFSA. Modern methodologies and tools for human hazard assessment of chemicals. 12.
823 EFSA Journal, Parma, 2014, pp. 13.
824 EFSA. Harmonisation of human and ecological risk assessment of combined exposure to
825 multiple chemicals. EN- 784. EFSA supporting publication, Parma, 2015, pp. 39.
826 Forbes VE, Calow P. Is the per capita rate of increase a good measure of population-level
827 effects in ecotoxicology? Environmental Toxicology and Chemistry 1999; 18: 1544-
828 1556.
829 Forbes VE, Calow P, Grimm V, Hayashi T, Jager T, Palmqvist A, et al. Integrating population
830 modeling into ecological risk assessment. Integrated Environmental Assessment
831 and Management 2010; 6: 191-193.
832 Goussen B, Beaudouin R, Dutilleul M, Buisset-Goussen A, Bonzom J-M, Péry ARR. Energy-
833 based modelling to assess effects of chemicals on Caenorhabditis elegans: A case
834 study on uranium. Chemosphere 2015; 120: 507-514.
835 Grech A, Brochot C, Dorne J-L, Quignot N, Bois FY, Beaudouin R. Toxicokinetic models and
836 related tools in environmental risk assessment of chemicals. Science of The Total
837 Environment.

838 Heard MS, Baas J, Dorne J-L, Lahive E, Robinson AG, Rortais A, et al. Comparative toxicity
839 of pesticides and environmental contaminants in bees: Are honey bees a useful
840 proxy for wild bee species? Science of The Total Environment 2017; 578: 357-365.
841 Hendriks AJ, Heikens A. The power of size. 2. Rate constants and equilibrium ratios for
842 accumulation of inorganic substances related to species weight. Environmental
843 Toxicology and Chemistry 2001; 20: 1421-1437.
844 Hendriks AJ, van der Linde A, Cornelissen G, Sijm DTHM. The power of size. 1. Rate
845 constants and equilibrium ratios for accumulation of organic substances related
846 to octanol-water partition ratio and species weight. Environmental Toxicology and
847 Chemistry 2001; 20: 1399-1420.
848 Hesketh H, Lahive E, Horton AA, Robinson AG, Svendsen C, Rortais A, et al. Extending
849 standard testing period in honeybees to predict lifespan impacts of pesticides and
850 heavy metals using dynamic energy budget modelling. Scientific Reports 2016; 6:
851 37655.
852 Hewlett PS, Plackett RL. A Unified Theory for Quantal Responses to Mixtures of Drugs:
853 Non-Interactive Action. Biometrics 1959; 15: 591-610.
854 Jager T, Albert C, Preuss TG, Ashauer R. General unified threshold model of survival - A
855 toxicokinetic-toxicodynamic framework for ecotoxicology. Environmental Science
856 and Technology 2011; 45: 2529-2540.
857 Jager T, Barsi A, Ducrot V. Hormesis on life-history traits: is there such thing as a free
858 lunch? Ecotoxicology (London, England) 2013a; 22: 263-70.
859 Jager T, Barsi A, Hamda NT, Martin BT, Zimmer EI, Ducrot V. Dynamic energy budgets in
860 population ecotoxicology: Applications and outlook. Ecological Modelling 2014a;
861 280: 140-147.
862 Jager T, Crommentuijn T, van Gestel CA, Kooijman SA. Simultaneous modeling of multiple
863 end points in life-cycle toxicity tests. Environ Sci Technol 2004; 38: 2894-900.
864 Jager T, Gudmundsdóttir EM, Cedergreen N. Dynamic Modeling of Sublethal Mixture
865 Toxicity in the Nematode Caenorhabditis elegans. Environmental Science &
866 Technology 2014b; 48: 7026-7033.
867 Jager T, Heugens EHW, Kooijman SALM. Making sense of ecotoxicological test results:
868 Towards application of process-based models. Ecotoxicology 2006; 15: 305-314.
869 Jager T, Klok C. Extrapolating toxic effects on individuals to the population level: the role
870 of dynamic energy budgets. Philosophical Transactions of the Royal Society B
871 2010a; 365: 3531-3540.
872 Jager T, Klok C. Extrapolating toxic effects on individuals to the population level: the role
873 of dynamic energy budgets. Philosophical Transactions of the Royal Society B:
874 Biological Sciences 2010b; 365: 3531-3540.
875 Jager T, Kooijman SALM. A biology-based approach for quantitative structure-activity
876 relationships (QSARs) in ecotoxicity. Ecotoxicology 2009; 18: 187-196.
877 Jager T, Martin BT, Zimmer EI. DEBkiss or the quest for the simplest generic model of
878 animal life history. Journal of Theoretical Biology 2013b; 328: 9-18.
879 Jager T, Salaberria I, Hansen BH. Capturing the life history of the marine copepod Calanus
880 sinicus into a generic bioenergetics framework. Ecological Modelling 2015; 299:
881 114-120.

Jager T, Vandenbrouck T, Baas J, De Coen WM, Kooijman SALM. A biology-based approach for mixture toxicity of multiple endpoints over the life cycle. Ecotoxicology 2010; 19: 351-361.
Jager T, Zimmer EI. Simplified Dynamic Energy Budget model for analysing ecotoxicity data. Ecological Modelling 2012; 225: 74-81.
Kienzler A, Barron MG, Belanger SE, Beasley A, Embry MR. Mode of Action (MOA) Assignment Classifications for Ecotoxicology: An Evaluation of Approaches. Environmental Science & Technology 2017; 51: 10203-10211.
Klanjscek T, Caswell H, Neubert MG, Nisbet RM. Integrating dynamic energy budgets into matrix population models. Ecological Modelling 2006; 196: 407-420.
Klanjscek T, Nisbet RM, Priester JH, Holden PA. Modeling Physiological Processes That Relate Toxicant Exposure and Bacterial Population Dynamics. PLoS ONE 2012; 7: e26955.
Klok C, Hjorth M, Dahllöf I. Qualitative use of Dynamic Energy Budget theory in ecotoxicology: Case study on oil contamination and Arctic copepods. Journal of Sea Research 2012; 73: 24-31.
Knapen D, Vergauwen L, Villeneuve DL, Ankley GT. The potential of AOP networks for reproductive and developmental toxicity assay development. Reproductive Toxicology 2015; 56: 52-55.
Kooi BW, van der Meer J. Bifurcation theory, adaptive dynamics and dynamic energy budget-structured populations of iteroparous species. Philosophical Transactions of the Royal Society B: Biological Sciences 2010; 365: 3579-3590.
Kooijman B, Lika D, Pecquerie L, Augustine S. Add-my-Pet, 2017.
Kooijman SALM. Dynamic Energy Budget theory for metabolic organisation. Cambridge: Cambridge University Press, 2010.
Kooijman SALM. Energy budgets: University of California press, 2012.
Kooijman SALM, Bedaux JJM. Analysis of toxicity tests on Daphnia survival and reproduction. Water Research 1996; 30: 1711-1723.
Kooijman SALM, Metz JAJ. On the dynamics of chemically stressed populations: The deduction of population consequences from effects on individuals. Ecotoxicology and Environmental Safety 1984; 8: 254-274.
Kooijman SALM, Sousa T, Pecquerie L, Van Der Meer J, Jager T. From food-dependent statistics to metabolic parameters, a practical guide to the use of dynamic energy budget theory. Biological Reviews 2008; 83: 533-552.
Kooijman SALM, Van Der Hoeven N, Van Der Werf DC. Population Consequences of a Physiological Model for Individuals. Functional Ecology 1989; 3: 325-336.
Lewis KA, Tzilivakis J, Warner DJ, Green A. An international database for pesticide risk assessments and management. Human and Ecological Risk Assessment: An International Journal 2016; 22: 1050-1064.
Lika K, Augustine S, Pecquerie L, Kooijman SALM. The bijection from data to parameter space with the standard DEB model quantifies the supply–demand spectrum. Journal of Theoretical Biology 2014; 354: 35-47.
Lika K, Kearney MR, Freitas V, van der Veer HW, van der Meer J, Wijsman JWM, et al. The "covariation method" for estimating the parameters of the standard Dynamic

926 Energy Budget model I: Philosophy and approach. Journal of Sea Research 2011a;
927 66: 270-277.
928 Lika K, Kearney MR, Kooijman SALM. The “covariation method” for estimating the
929 parameters of the standard Dynamic Energy Budget model II: Properties and
930 preliminary patterns. Journal of Sea Research 2011b; 66: 278-288.
931 Lopes C, Péry ARR, Chaumot A, Charles S. Ecotoxicology and population dynamics: Using
932 DEBtox models in a Leslie modeling approach. Ecological Modelling 2005; 188: 30-
933 40.
934 Margerit A, Gomez E, Gilbin R. Dynamic energy-based modeling of uranium and cadmium
935 joint toxicity to Caenorhabditis elegans. Chemosphere 2016; 146: 405-12.
936 Margerit A, Lecomte-Pradines C, Svendsen C, Frelon S, Gomez E, Gilbin R. Nested
937 interactions in the combined toxicity of uranium and cadmium to the nematode
938 Caenorhabditis elegans. Ecotoxicology and Environmental Safety 2015; 118: 139-
939 148.
940 Martin B, Jager T, Nisbet RM, Preuss TG, Grimm V. Limitations of extrapolating toxic
941 effects on reproduction to the population level. Ecological Applications 2014; 24:
942 1972-1983.
943 Martin BT, Jager T, Nisbet RM, Preuss TG, Hammers-Wirtz M, Grimm V. Extrapolating
944 ecotoxicological effects from individuals to populations: a generic approach based
945 on Dynamic Energy Budget theory and individual-based modeling. Ecotoxicology
946 2013; 22: 574-583.
947 Martin BT, Zimmer EI, Grimm V, Jager T. Dynamic Energy Budget theory meets individual-
948 based modelling: a generic and accessible implementation. Methods in Ecology
949 and Evolution 2012; 3: 445-449.
950 Meek ME, Palermo CM, Bachman AN, North CM, Jeffrey Lewis R. Mode of action human
951 relevance (species concordance) framework: Evolution of the Bradford Hill
952 considerations and comparative analysis of weight of evidence. Journal of Applied
953 Toxicology 2014; 34: 595-606.
954 Meer Jvd. An introduction to Dynamic Energy Budget (DEB) models with special emphasis
955 on parameter estimation. Journal of Sea Research 2006; 56: 85-102.
956 Muller E, Nisbet R, Berkley H. Sublethal toxicant effects with dynamic energy budget
957 theory: model formulation. Ecotoxicology 2010a; 19: 48-60.
958 Muller E, Osenberg C, Schmitt R, Holbrook S, Nisbet R. Sublethal toxicant effects with
959 dynamic energy budget theory: application to mussel outplants. Ecotoxicology
960 2010b; 19: 38-47.
961 Muller EB, Hanna SK, Lenihan HS, Miller RJ, Nisbet RM. Impact of engineered zinc oxide
962 nanoparticles on the energy budgets of Mytilus galloprovincialis. Journal of Sea
963 Research 2014; 94: 29-36.
964 Newman MC, McCloskey JT. The individual tolerance concept is not the sole explanation
965 for the probit dose-effect model. Environmental Toxicology and Chemistry 2000;
966 19: 520-526.
967 Nisbet RM, McCauley E, Johnson LR. Dynamic energy budget theory and population
968 ecology: lessons from Daphnia. Philosophical Transactions of the Royal Society of
969 London B: Biological Sciences 2010; 365: 3541-3552.

970 OECD. Current approaches in the statistical analysis of ecotoxicity data: a guidance to
971 application. In: OECD, editor. OECD Series on Testing Assessment. 54. Organisation
972 for Economic Cooperation and Development, Paris, 2006.
973 Poggiale J-C, Baklouti M, Queguiner B, Kooijman SALM. How far details are important in
974 ecosystem modelling: the case of multi-limiting nutrients in phytoplankton–
975 zooplankton interactions. Philosophical Transactions of the Royal Society of
976 London B: Biological Sciences 2010; 365: 3495-3507.
977 Robinson A, Hesketh H, Lahive E, Horton AA, Svendsen C, Rortais A, et al. Comparing bee
978 species responses to chemical mixtures: Common response patterns? PLOS ONE
979 2017; 12: e0176289.
980 Schultz CL, Wamucho A, Tsyusko OV, Unrine JM, Crossley A, Svendsen C, et al.
981 Multigenerational exposure to silver ions and silver nanoparticles reveals
982 heightened sensitivity and epigenetic memory in Caenorhabditis elegans.
983 Proceedings of the Royal Society of London B: Biological Sciences 2016; 283.
984 Sousa T, Domingos T, Poggiale JC, Kooijman SALM. Dynamic energy budget theory
985 restores coherence in biology. Philosophical Transactions of the Royal Society B:
986 Biological Sciences 2010; 365: 3413-3428.
987 Spurgeon DJ, Jones OAH, Dorne J-LCM, Svendsen C, Swain S, Stürzenbaum SR. Systems
988 toxicology approaches for understanding the joint effects of environmental
989 chemical mixtures. Science of The Total Environment 2010; 408: 3725-3734.
990 Teeguarden JG, Tan Y-M, Edwards SW, Leonard JA, Anderson KA, Corley RA, et al.
991 Completing the Link between Exposure Science and Toxicology for Improved
992 Environmental Health Decision Making: The Aggregate Exposure Pathway
993 Framework. Environmental science & technology 2016a; 50: 4579-4586.
994 Teeguarden JG, Tan Y-M, Edwards SW, Leonard JA, Anderson KA, Corley RA, et al.
995 Completing the Link between Exposure Science and Toxicology for Improved
996 Environmental Health Decision Making: The Aggregate Exposure Pathway
997 Framework. Environmental Science & Technology 2016b; 50: 4579-4586.
998 US-EPA. ECOTOX User Guide: ECOTOXicology Database System. Version 4.0. Available:
999 http:/www.epa.gov/ecotox/. US EPA, 2013.
1000 Villeneuve DL, Crump D, Garcia-Reyero N, Hecker M, Hutchinson TH, LaLone CA, et al.
1001 Adverse Outcome Pathway (AOP) Development I: Strategies and Principles.
1002 Toxicological Sciences 2014a; 142: 312-320.
1003 Villeneuve DL, Crump D, Garcia-Reyero N, Hecker M, Hutchinson TH, LaLone CA, et al.
1004 Adverse Outcome Pathway Development II: Best Practices. Toxicological Sciences
1005 2014b; 142: 321-330.
1006 VU-Theoretical-Biology. Add my pet, Vrije-Universiteit-of-Amsterdam, 2017.
1007 Wren J, Kille P, Spurgeon D, Swain S, Sturzenbaum S, Jager T. Application of physiologically
1008 based modelling and transcriptomics to probe the systems toxicology of aldicarb
1009 for Caenorhabditis elegans (Maupas 1900). Ecotoxicology 2011; 20: 397-408.
1010 Zimmer E, Jager T, Ducrot V, Lagadic L, Kooijman SALM. Juvenile food limitation in
1011 standardized tests: a warning to ecotoxicologists. Ecotoxicology 2012; 21: 2195-
1012 2204.

1013 Zitko V. An equation of lethality curves in tests with aquatic fauna. CHEM</cja:jid>
1014 Chemosphere 1979; 8: 47-51.
1015
1016